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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HUMAN GENOME SCIENTISTS, INC.
9410 KEY WEST AVENUE
ROCKVILLE MD 20850

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 07/13/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed onthe election of 10/29/99☐ This action is FINAL.☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 18-19, 21-22, 37-39, 41, 42-94 is/are pending in the application.Of the above, claim(s) 1, 18-19, 21-22, 37-39, 41 is/are withdrawn from consideration.☐ Claim(s) _____ is/are allowed.☒ Claim(s) 72-94 is/are rejected.☐ Claim(s) _____ is/are objected to.☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.☐ The drawing(s) filed on _____ is/are objected to by the Examiner.☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.☐ The specification is objected to by the Examiner.☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been☐ received.☐ received in Application No. (Series Code/Serial Number) _____☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____☐ Interview Summary, PTO-413☒ Notice of Draftsperson's Patent Drawing Review, PTO-948☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

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1. Part III: Detailed Office Action

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

2. Formal Matters:

In view of the papers filed 10-29-99, the inventorship in this nonprovisional application has been changed by the deletion of Jun Zhang.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Furthermore, applicants change to the specification to correct for the hybridization conditions and the explanations provided for such are sufficient to make this change. Correction of other typographical errors have also been entered.

3. Restriction Requirement:

First of all, for clarification of record, the following is a summary of the claims of record and those that represent the elected inventive group. Newly presented claims 42-94 are directed to the TNF- γ -alpha(α), and represent the elected groups.. Claims 1, 18-19, 21-22, 37-39 and 41 are directed to non-elected groups.

Applicant's election with traverse of Group II, now claims 42-94 in Paper No. 6 of 10/1999 is acknowledged. The traversal is on the ground(s) that there would not be a serious burden to search and examine the groups together because art that disclose nucleic acid generally disclose amino acid sequence for the encoded protein. This is not found persuasive because most contrary to applicants position, the mere search of each of the 10 groups would be a tremendous burden in both the scientific literature as well as in the various classes and subclasses. Also, protein, nucleic acids, antibodies and other products are not classified in the same areas and this is true for the various methods claims as well. The examination of each of the 10 groups would also

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pose a serious burden on the Examiner, given the amount of time that an Examiner is allotted to complete an applications. Therefore, the search and examination of 10 clearly distinct groups would pose a serious burden on the Examiner, as the searches are not co-extensive.

The requirement is still deemed proper and is therefore made FINAL.

4. Objections and 112 Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42d, 42h, 49-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full length nucleic acids and the encoded protein therefrom, does not reasonably provide enablement for : 1) any fragment that many have TNF- γ alpha activity (cl=42d, 42h, 49-54, 55-64, 65-74); 2) nor is there enablement for any 30 contiguous nucleic acids that will encode for about any 10 contiguous amino acid sequence (cl=55-64), or any 30 contiguous amino acids (cl= 65-74); 3) there is lack of enablement for any fragment that binds an antibody to TNF- γ alpha (cl=49, 51, 58, 61, 68, 71, 79, 82, 85, 91; 4) to heterologous sequence or heterologous sequence that encodes for any polypeptide that is linked to the claimed nucleic acid sequence (cl=52, 62, 72, 86, 92). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success the invention commensurate in scope with these claims.

The elected inventive group is directed to the mature TNF- γ alpha and to various fragments, contiguous portions and potentially modified forms (as encompassed by claims 75-88 which define the protein in terms of percent identity). As a result, these various claims are being rejected as being non-enabling for the full scope of the claims as has been enumerated by the four different reasons that the claims are not enabled by the specification's teachings. The lack of

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enablement for these claims are similar and will be addressed together, especially for fragments and contiguous sequences, based on the fact that the specification has not provided sufficient enablement in the form of examples, evidence or guidance for the entire scope of these claims. Although the various portions of claims 42-61 state that the fragment has to either have TNF- γ alpha activity or bind to an antibody that is specific to the TNF- γ alpha, the presence of this functional limitation in the claims is still not commensurate in scope with the teachings in the specification.

The specification makes general reference to fragments (presumably from proteolytic cleavage or chemical synthesis if the encoded protein); however, this does not serve to enable the scope of the claims. The skilled artisan would be faced with an undue amount of experimentation for determining how long the encoded fragment must be; from what region/portion on the encoded protein the fragment covers, represents or corresponds to; does the encoded fragment have to represent a contiguous string of amino acid residues on the encoded protein's structure; because knowledge of these variables with assurances that the fragment is biologically active for regulating endothelial cell growth must be provided in order to satisfy the requirement for enablement. Furthermore, the claims do not set forth any specific fragments that are identified by their size, specific amino acids residues, nor to the specific region on the protein that this fragment correspond to (e.g. the N- or C-terminal regions; if it is a fragment from an internal portion of the protein and what this specific portion is).

Applicants can not merely rely on the issue of "make and test" to satisfy the enablement provisions for the breadth of the fragments or contiguous residues presented in the claims. Rather, the skilled artisan would need to necessarily know how to make and use the specific fragments with reasonable assurance that the fragment would possess the desired activity and can be usable as such. In a likewise manner, there are limited structure/function studies provided of record for the protein which, if present, would serve to enable the scope of the fragments or contiguous residues. Thus, the skilled artisan is without guidance for determining if the

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contiguous amino acids have to represent certain functionally active regions and where such specific nucleic acids are that would encode for such things as the binding regions, and there is it is a lack of enablement and guidance for where usable epitopic/antigenic regions are from the encoded nucleic acids; and for whether the fragments or contiguous regions correspond to regions of thermal or enzymatic activity, or other stability regions; and there is a lack of enablement for the necessity of the nucleic acids that encode for the N-and C-terminals and a clear lack of teachings for how this is determined.

Even though in Figure 17, applicants attempt to provide the analysis of the protein for such things as antigenic index (via Jameson-Wolf), α and β turns/regions (via Garnier-Pobson, Chou-Fasman or Eisenberg); coil regions; hydrophilic, hydrophobic and amphipathic regions (via Kyte-Doolittle, Hopp-Woods or Eisenberg); flexible region (via Karplus-Schulz); surface probability (via Emini), and antigenic or epitopic regions-all via a computer program that does not expressly state the exact residue location, but rather merely estimate on these regions. Antigenic Index or Jameson-Wolf graph, presumably identify epitopic regions and in the brief description for this figures, applicants have listed peptide regions that they conclude are highly antigenic; however, a review of this figure and other statements in the specification does not make clear that the antigenic regions are for any specific amino acid residues, especially those that may be listed in the claims, because these teachings are not sufficiently precise enough to draw such conclusions that would satisfy the enablement provisions of the statute. In the absence of this, the specification has not provided sufficient evidence or examples or guidance to ensure that these regions are antigenic and that antibodies could be specifically elicited to these peptides. Since some of the claim limitations require that there is binding of the peptide to an antibody, there is insufficient evidence, nor would the skilled artisan expect that each of the encoded peptide regions would produce binding antibodies, whether agonist, antagonist, neutralizing etc. It is suggested that the claims be amended to delete reference to antigenic/epitopic regions and the reference to binding to antibodies. It is well known in the art that antibodies that bind to the full length protein possess

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different and distinct structural and functional characteristic from antibodies that bind to only certain portions of a protein's structure. Furthermore, it is also known that all small peptide portions do not elicit an antibody response and the affinity and specificity of binding depends on the size and make-up of the antigenic peptide. Thus, the use of one peptide regions of a given size does not necessarily predict that all other peptides derived from that protein can also bind to an antibody or elicit an antibody response. In the absence sufficient examples and guidance, the specification has not provided sufficient evidence or examples or guidance to ensure that these regions are even antigenic in nature and sufficient to elicit an antibodies response.

While it well settled that a specification need not contain examples in order to be enabling, however, in the express absence of such, the specification must provide enablement alternatively in the form of evidence or guidance. It is also known and accepted that examples, evidence of guidance are not required if, on its face, it is clear to the skilled artisan that the claims are enabled; and when there is no reason to question the objective truths of applicant's mere statement of assertions that the DNA that defines the various protein fragments or contiguous regions are enabled by the specification. In addition to there being insufficient examples, the specification is also devoid of sufficient evidence or guidance that would serve to enable the claims. For example, at pages various pages of the specification, applicant have merely set forth general statements about variants, polypeptides and modifications, fragmentation, biological activity of the full length protein (Figures 7-16); and have cited general teaching reference that appear to merely represent "boiler plate" teaching for how to achieve such modifications. However, what is not taught is the nexus or relation that these would have to the various modified amino acids and the resulting functionality of the protein that would serve to enable the full scope of the claims for how to make and use these various portions of the nucleic acids that would encode for any and every conceivable portion of the TNF- γ protein without having to encounter undue experimentation.

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For instance, even though applicants have provided the nucleic acid and amino acid sequence for the TNF- γ , and have further concluded that the biological properties associated with this presumably novel protein would be similar to that of other TNF proteins, there are limited structure/function studies that would lead the skilled artisan to the region or specific amino acid residues that are responsible for a certain functional activity or a functional activity that could be usable, while still possessing the desired activity. Furthermore, while the structural identity of the novel TNF- γ may be similar to the TNF proteins, this amounts to limited homology, and the mere existence of structural similarity does not, in and of itself, always equate to the same or similar functional activity. In fact, it is known that there could exist drastic differences in the functionality of structurally-similar proteins. Further, in the absence of these structure/function studies for the protein and certainly for the fragments and contiguous regions, the skilled artisan would not know, absent sufficient examples, evidence or guidance, where to start selecting residues and how long the regions would have to be to obtain the scope of the claims with assurance that they are functionally active and usable regions. In view of all of the above, the skilled artisan would encounter undue experimentation to achieve the scope of these claims, because there also does not appear to be a sufficiently established and reproducible assay for determining the biological activity that applicants desire to be associated with the protein fragments or contiguous regions.

Since there is insufficient enablement for where the biologically active regions are, it would be difficult to determine what specific functional activity on the protein these fragments or contiguous amino acids cover since many proteins possess multiple biological activities. All of these variables would have to be known for the skilled artisan to produce nucleic acids for the encoded fragments or contiguous encoded regions that possess the desired properties and therefore be usable in a manner contemplated. Without such information, the skilled artisan would have to resort to trial-and-error and be faced with undue experimentation for making and using the full scope of these fragments based on the limited characterization set forth in the

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specification, as well as the limited characterization that has been set forth in the claims for the fragments or contiguous.

The specification fails to teach what specific residues of the amino acid sequence the activity corresponds to for either the fragments or the contiguous regions, because applicants have merely provided a definition for "fragment" and recited very general and non-specific way of obtaining the fragments, thus, based on all of the other reasons set forth above the artisan would encounter undue experimentation in order to practice the scope of these claims. In the absence of specific examples, in order to satisfy the enablement provision to support the scope of the claims, alternatively, applicants should provide evidence and/or guidance to enable the scope of these fragments. But the specification is devoid of such teachings as well. So, in the absence of such, the skilled artisan would be faced with undue experimentation for trying to determine how and where to start to make the full scope of the polynucleotides to encode for fragments or contiguous amino acids as recited by the claims. Enablement for the claims can not merely be perfected by the general reference to cleaving the protein from one or both ends to obtain a biologically protein. There must be some guidance, the establishment of a nexus or a reasonable degree of predictability about where these regions are and how to obtain a fragment or contiguous region of sufficient size that could be used for its intended purpose.

The specification is also non-enabling for any heterologous sequence fused the nucleic acid that encodes for the mature protein or portions thereof. The scope of this term encompasses nucleic acid sequences that do not encode for protein as well as nucleic acids where the sequence is responsible for expression of the protein. The nature and make-up of these heterologous sequence bears an importance on the expression and functionality of the encoded protein products, thus, without sufficient examples and guidance for the need of this heterologous sequence, the artisan would again be faced with undue experimentation for selection a sequence that would work in conjunction with the structure and function of nucleic acid sequence and the encoded protein sequence. Heterologous sequence or protein represent a broad category, such

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that a lack of guidance for the appropriate sequence that could function in a manner desired by the claims would have to be set forth in the specification in order to enable the scope of the claims. It is also pointed out that some of the other positions stated above in this lack of enablement rejections would also apply for the lack of enablement for heterologous sequences fused to the TNF- γ .

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite and/or confusing based on the specification. While all of the elected claims appear to be directed to the alpha (α) form of TNF-gamma (γ), it is not exactly clear from the specification which Seq ID is the alpha or beta form of TNF- γ . At several pages in the specification, applicants indicate that the alpha form is that in Seq ID No 1 and 2 for the nucleic acid and amino acid sequence respectively and that it also corresponds to the deposit of 1994 (page 4+), and that the beta form of TNF- γ has the sequence of ID No 20 and was deposited in 1998 (page 4-5); yet at several other places in the specification (e.g. bottom of page 8,) applicants states that the alpha form is that in Seq ID No 20. This is truly contradictory as the alpha form can not be that in Seq ID No 1-2, as well as that in Seq ID No 20 because these two set of Seq ID's differ. At page 6 of the specification, applicants state that the alpha form of the protein refers to clone 2033055, which was deposited in 1998, but earlier statements indicate that the alpha form of the protein is associated with the clone that was deposited in 1994-namely clone number 75927. Correction and/or clarification is requested without introducing new matter; and the entire specification should be review and corrected accordingly.

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The specification also renders the claims confusing or contradictory in referring to the protein as TNF- γ - α , but several of the figures uses VEGI. There should be consistency in the terms used to identify and claim applicants product. Further, based on the statements in the specification, when the figures use VEGI, it is not sure if this refers to the alpha or beta form of TNF- γ . Again, corrections and/or clarification is requested without the introduction of new matter.

Claims 75-88 are indefinite and confusing in the manner in which the claims is drafted, because it is not clear if the alternative embodiments of the Markush group defines the first polynucleotide or the second nucleotide. Thus, it is requested that the claims be amended to more precisely define and claim the inventive concept to which the claims are intended to be drafted.

5. Art Rejections:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 55-94 are rejected under 35 U.S.C. 102() as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Burns et al, Lowe, or Cullen et al.

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The claims are directed to various portions a protein that is either encoded by 30 contiguous nucleotides; or to fragments of the protein; or to 30 contiguous amino acid residues; or to peptides that are encoded by nucleic acid molecules that will hybridize to the sequence in Seq ID No. 1. Some of these claims recite a functionality for the peptide, although very vague and general in nature, but some of the other claims do not recite a functional activity for the claimed protein portions.

The prior art discloses nucleic acid sequences that encode for a functionally active protein, despite the fact that the proteins are referred to by different names (see the sequence alignment). Since the size of the amino acid regions of the prior art proteins meet the limitations of these claims, in the express absence of the prior art to disclose any functional activity, one skilled in the art would reasonably expect that identical peptide regions would possess the same or substantially similar functional activity (i.e. TNF- γ alpha activity or antibody binding activity). According to the sequence alignments between the prior art and claimed nucleic acids, there is sufficient sequence identity that would allow the claimed nucleic acids to hybridize to the prior art sequences, or they also satisfy the claim limitation of being at least 30 contiguous nucleotides. Thus, the instant claims are anticipated by the prior art or at least rendered prima facie obvious therefrom, and the burden is upon applicants to establish a patentable difference (In re Best 195 USPQ 430).

6. Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1647, whose telephone number is (703) 308-4232**. Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to 6:00 P.M.

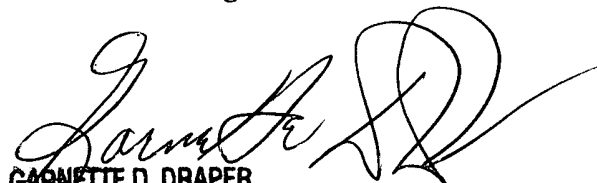
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax

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Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.


GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800